# Quantitative Morphology of the Caudate Nucleus in Attention Deficit Hyperactivity Disorder

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*Objective:* *Because the caudate nuclei receive inputs from cortical regions implicated in executive functioning and attentional tasks, caudate and total brain volumes were examined in boys with attention deficit hyperactivity disorder (ADHD) and normal comparison subjects. To gain developmental perspective, a wide age range was sampled for both groups.* *Method:* *The brains of 50 male ADHD patients (aged 6–19) and 48 matched comparison subjects were scanned by magnetic resonance imaging (MRI). Volumetric measures of the head and body of the caudate nucleus were obtained from $T_1$-weighted coronal images. Interrater reliabilities (intraclass correlations) were 0.89 or greater.* *Results:* *The normal pattern of slight but significantly greater right caudate volume across all ages was not seen in ADHD. Mean right caudate volume was slightly but significantly smaller in the ADHD patients than in the comparison subjects, while there was no significant difference for the left. Together these facts accounted for the highly significant lack of normal asymmetry in caudate volume in the ADHD boys. Total brain volume was 5% smaller in the ADHD boys, and this was not accounted for by age, height, weight, or IQ. Smaller brain volume in ADHD did not account for the caudate volume or symmetry differences. For the normal boys, caudate volume decreased substantially (13%) and significantly with age, while in ADHD there was no age-related change.* *Conclusions:* *Along with previous MRI findings of low volumes in corpus callosum regions, these results support developmental abnormalities of frontal-striatal circuits in ADHD.*

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Attention deficit hyperactivity disorder (ADHD), the most common psychiatric disorder of childhood and adolescence, is characterized by deficits in attentional performance, especially on vigilance tasks and during effortful attention, as well as by motor hyperactivity, impulsivity, and distractibility. Numerous twin, adoption, and family studies suggest a strong familial component to the transmission of ADHD, having a pattern consistent with autosomal dominant transmission (1–3). Functional imaging techniques used to pinpoint the specific anatomic substrates of ADHD have implicated striatal hypoperfusion (4, 5) and low global glucose metabolism (6), particularly in frontal regions. However, subsequent work with positron emission tomography (PET) has yielded inconsistent results across techniques, ages, sex, or effects of individual stimulants (7–9).

In contrast to PET, anatomic investigations in ADHD using magnetic resonance imaging (MRI) offer the advantage of high-resolution images without ionizing radiation, making MRI ideal for obtaining information about the developing human brain, both normal and pathological.

Preliminary studies have suggested anatomical brain abnormalities in ADHD. Hynd et al. (10) found that 10 children with ADHD lacked the expected asymmetry in single-slice axial measurements of the width of the anterior cerebral cortices. In another study, Hynd's group (11) found the corpus callosum of seven children with ADHD to be smaller than that of 10 comparison subjects (although the comparison subjects were on average 2.7 years older). Recently, two anterior subregions of the corpus callosum, the rostrum and rostral body, were found to be smaller in 18 boys with ADHD than in 18 matched comparison subjects, and these differences in cross-sectional area correlated significantly

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**TABLE 1. Demographic and Behavioral Measures for 50 Boys With Attention Deficit Hyperactivity Disorder (ADHD) and 48 Matched Normal Boys**

| Measure | ADHD | | Normal | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 12.3 | 3.1 | 12.1 | 3.0 |
| Height (in) | 60.9 | 7.1 | 60.8 | 7.5 |
| Weight (lb) | 101.9 | 38.1 | 101.6 | 34.0 |
| Tanner stage | 2.6 | 1.7 | 2.4 | 1.6 |
| WISC-R subscales | | | | |
| Vocabulary[a] | 11.7 | 2.9 | 13.8 | 2.7 |
| Block design[b] | 11.6 | 3.6 | 13.8 | 2.7 |
| Continuous Performance Test errors | | | | |
| Omission | 19.6 | 19.5 | — | — |
| Commission | 25.2 | 31.0 | — | — |
| Conners Teachers Rating Scale hyperactivity ratings[c] | | | | |
| Teacher | 1.68 | 0.65 | — | — |
| Parent | 1.98 | 0.76 | — | — |

[a]Significant difference between 47 ADHD boys and 46 normal boys (t=3.54, df=91, p=0.0006, two-tailed).
[b]Significant difference between 47 ADHD boys and 46 normal boys (t=3.22, df=91, p=0.002, two-tailed).
[c]Maximum score=3.0.

with a measure of classroom hyperactivity (12). Hynd et al. (13) also recently reported that 11 children with ADHD had abnormal caudate asymmetry, compared to 11 comparison subjects on a single "best view" axial slice of the anterior horns of the lateral ventricles. However, single-slice measures of symmetry are difficult to interpret, so the reproducibility of this finding is not yet established. However, the hypothesis of caudate nuclei involvement in ADHD is of interest because the caudates receive many of their inputs from the dorsolateral and orbitofrontal cortices (14), which have been found to subserve functions that are aberrant in children with ADHD (15–18).

To more carefully define the role of striatal asymmetry in the pathophysiology of ADHD, we examined caudate volumes and asymmetry in a large group of ADHD and normal boys. To gain developmental perspective, subjects from a wide age span, 5 to 19 years, were recruited.

## METHOD

### *Subjects*

Eighteen subjects from each of the groups defined in the following were the basis of an earlier report (12).

The ADHD group consisted of 50 boys (age range=6.4–19.5) recruited from a National Institute of Mental Health (NIMH) day treatment program. The inclusion criteria included a history of hyperactive, inattentive, and impulsive behaviors that were impairing in at least two settings (home, school, or day program), confirmed by a Conners Teachers Rating Scale hyperactivity rating greater than two standard deviations beyond the mean for age. Thirty-nine of the 50 patients had been previously treated with psychostimulants, and all patients participated in a 12-week double-blind trial of methylphenidate, *d*-amphetamine, and placebo, which is described elsewhere (19). All the children had prominent motor restlessness and impulsivity, and approximately 80% were strikingly clinically inattentive. The diagnoses of attention deficit disorder with hyperactivity and ADHD were established according to DSM-III and DSM-III-R criteria, respectively, on the basis of a structured interview, the Diagnostic Interview for Children and Adolescents (20), with a parent and the patient and a battery of standardized parent and teacher rating scales, including those named in the next section. The exclusion criteria were a full-scale IQ less than 80 on the Wechsler Intelligence Scale for Children—Revised (WISC-R), evidence of medical or neurological disorders on examination or by history, Tourette's syndrome, or any other axis I psychiatric disorder, with the exception of conduct disorder (N=8) or oppositional defiant disorder (N=21). Thirteen subjects had specific developmental disorders (math and/or reading) confirmed by comparison with WISC-R and Woodcock-Johnson Psychoeducational Battery (21) standard scores.

The comparison subjects were 48 healthy boys (age range=5.5–17.8) matched for age, weight, height, Tanner stage, and handedness who were recruited from the community. Matching body size (22) and developmental stage (23) was important, as these might be related to brain structure size. Individuals with medical disorders, neurological disorders, lifetime histories of psychiatric disorders, or first-degree relatives with major psychiatric disorders, including ADHD, were excluded.

The study was explained to the subjects and their parents, and assent from the child and written consent from the parents were obtained. The protocol was approved by the institutional review board at NIMH.

Of the 50 patients with ADHD, 86% were right-handed (N=43), 10% were left-handed (N=5), and 4% had mixed handedness (N=2). Of the comparison subjects, 90% were right-handed (N=43) and 10% were left-handed (N=5). Table 1 presents other demographic characteristics of the two groups. There were no significant group differences in age, height, or weight.

### *Behavioral Measures*

Behavioral measures for the patients were obtained after at least 4 weeks without psychoactive medications. The conduct and hyperactivity factors were extracted from the Conners Parents and Teachers Rating Scales (24). The Continuous Performance Test (25) yielded omission and commission errors. The full WISC-R was administered to all patients, and the comparison subjects were assessed with the vocabulary and block design subscales from the WISC-R. Scores on the WISC-R subscales, the Continuous Performance Test, and the Conners scales are shown in table 1. IQ differences were found on the WISC-R vocabulary and block design subtests; the comparison subjects scored significantly higher. However, the means of both groups on both subtests were above average (mean=10, SD=3).

Each subject also received a comprehensive assessment, including physical and neurological examination, child and parent interviews with the Diagnostic Interview for Children and Adolescents (20), and the 12 handedness items from the Revised Neurological Examination for Subtle Signs (26).

### *MRI Protocol and Image Analysis*

All subjects were scanned with a GE 1.5-T Signa scanner located at the National Institutes of Health (NIH) Clinical Center. Head alignment was standardized by placing vitamin E capsules, which emit a distinctive MRI signal, in each auditory meatus and on the left inferior orbital ridge. If all three vitamin E capsules were not present in a single axial slice, the subject was repositioned until this criterion was met. Volumetric measures of the caudate were obtained from $T_1$-weighted coronal images with a slice thickness of 2.0 mm by using three-dimensional spoiled gradient recalled echo in the steady state (time to echo=5 msec, repetition time=24 msec, flip angle=45°, acquisition matrix=192×256, number of excitations=1, field of view=24 cm). Sedation with chloral hydrate (2.0 g p.o.) was used when indicated for the ADHD group.

All scans were evaluated by a clinical neuroradiologist. No gross abnormalities were found for any subject. The images were transferred to a Macintosh II FX computer workstation and analyzed with an image analysis program (Image 1.46) developed at NIH (27).

The head and body of the caudate nuclei were manually outlined on every other 2.0-mm slice in which they were visible in the coronal plane. Those area measures were multiplied by the effective slice thickness of 4.0 mm to derive volumes. The coronal slice containing the interventricular foramina was deemed the most posterior section of the head of the caudate nucleus as defined in *Gray's Anatomy* (28). All caudate measurements were made by a neuroanatomist (P.E.) or a neuropsychiatrist (J.N.G.) who was blind to any identifying information, including diagnosis or age. Intrarater and interrater reliabilities (intraclass correlation, ICC) were 0.94 and 0.92 for the head of the caudate and 0.91 and 0.89 for the body, respectively.

Total brain volume was calculated by using a supervised thresholding technique to determine the area of all brain matter (excluding ventricles) on every other 1.5-mm axial section and multiplying by the effective slice thickness of 3.0 mm. The intrarater ICC was 0.99.

### *Statistical Analysis*

The dependent variables were volumetric measurements of the right and left caudates, defined as the sum of the head and body (excluding the tail). Right-left asymmetry was quantified by the formula (R–L)/[(R+L)/2]×100.

Volumetric and asymmetry measurements were analyzed with two-tailed t test, repeated-measures analysis of variance (ANOVA), and analysis of covariance (ANCOVA) to test the effects of possible confounders, such as age, IQ subscale scores, and total brain volume, by using SAS, version 6 (29). Duncan's multiple range test was used for post hoc tests. Pearson correlations between volumetric or asymmetry measures and behavioral or demographic variables were examined. Partial correlations, controlling for age, vocabulary subscore, and total brain volume, were obtained where indicated.

## RESULTS

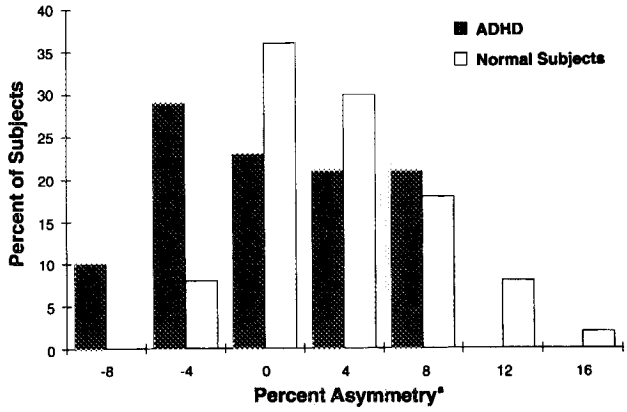
The mean total brain volume, as measured on axial scan, was 944.2 ml (SD=95.2) for the ADHD patients and 999.0 (SD=90.6) for the comparison group; the difference was significant (t=2.87, df=93, p=0.005). Total brain volume correlated significantly with caudate volume in both groups; for the comparison subjects (N=47) the correlations were r=0.59 (left) and r=0.65 (right), and for the patients (N=48) they were r=0.70 (left) and r=0.67 (right) (p=0.0001 for each).

### *Caudate Measures*

Caudate asymmetry was calculated by using the formula (R–L)/[(R+L)/2]×100 for each group. Thus, a positive asymmetry score indicates that the right caudate volume is greater than the left. As seen in figure 1, while there was overlap between the groups, the normal boys exhibited a higher mean asymmetry score (mean=3.7%, SD=4.4%) than the ADHD boys (mean=0.4%, SD=5.2%) (t=3.31, df=96, p=0.001). The range of caudate asymmetry for the normal subjects was –3.8% to 17.9%, and in the patients it was –10.5% to 9.4%. Caudate asymmetry was not related to age for either group (p>0.7).

Since the two groups differed on caudate asymmetry, the right-left differences within groups were assessed by paired t test. For the normal subjects the mean right caudate volume was 5.24 ml (SD=0.59) and the mean left caudate volume was 5.06 ml (SD=0.59), a significant difference (t=5.71, df=47, p=0.0001). For the ADHD patients the difference between the right side (mean=4.92 ml, SD=0.81) and the left side (mean=4.89 ml, SD=0.71) was not significant (t=0.89, df=49, p=0.43).

**FIGURE 1. Frequency Distribution of Caudate Asymmetry in 50 Boys With Attention Deficit Hyperactivity Disorder (ADHD) and 48 Matched Normal Boys**




[a]Percent asymmetry defined as (R–L)/[(R+L)/2]×100. A positive number indicates that the caudate volume on the right side is greater than that on the left side.

ANOVA was used to further examine this relationship by using the right and left caudate volumes directly (without transformation by the symmetry formula). The Side by Diagnosis interaction on ANOVA was significant (F=9.44, df=1, 96, p=0.003). Duncan's post hoc testing confirmed that for the normal subjects the right caudate was significantly larger than the left (p=0.05), while the right and left caudates were approximately the same size for the patients. Because of the group differences in total brain volume, an ANCOVA was also conducted with total brain volume as the covariate. The results did not change; the comparison subjects exhibited significantly more asymmetry (Side by Diagnosis interaction: F=6.00, df=1, 96, p=0.02).

The patients and comparison subjects also differed significantly in relation of brain volumes to scores on WISC-R subtests. The vocabulary subscore correlated significantly with total brain volume (r=0.33, N=46, p=0.02) but not with caudate volumes (right: r=0.22, N=46, p=0.14; left: r=0.26, N=46, p=0.08) in the normal subjects or in the ADHD boys (p>0.17).

### *Age Groups*

The patients and comparison subjects encompassed a wide age range (5–19 years). To assess the relationship of age to asymmetry, the groups were divided into age quartiles (5.5–8.3, 8.4–11.5, 11.6–14.6, and 14.7–19.5 years). A 2×4×2 ANOVA (Side by Age by Diagnosis) showed a significant interaction (table 2). An ANCOVA, with total brain volume as the covariate, remained significant. Side by Diagnosis ANOVAs within each age group revealed significant asymmetry differences in the oldest and youngest age groups (p=0.01 and 0.05, respectively), a trend in the third oldest (p=

**TABLE 2. Right and Left Caudate Volumes in Boys With Attention Deficit Hyperactivity Disorder (ADHD) and Matched Normal Boys, by Age Quartile[a]**

| | | Volume (ml) | | | |
|---|---|---|---|---|---|
| | | Right | | Left | |
| Group | N | Mean | SD | Mean | SD |
| ADHD | — | — | — | — | — |
| 5.5–8.3 years | 5 | 4.7 | 0.8 | 4.9 | 0.7 |
| 8.4–11.5 years | 15 | 5.1 | 1.0 | 4.9 | 0.8 |
| 11.6–14.6 years | 20 | 4.9 | 0.7 | 4.8 | 0.6 |
| 14.7–19.5 years | 8 | 4.9 | 1.0 | 5.0 | 0.9 |
| Normal | — | — | — | — | — |
| 5.5–8.3 years | 5 | 5.9 | 0.6 | 5.6 | 0.6 |
| 8.4–11.5 years | 17 | 5.3 | 0.4 | 5.2 | 0.4 |
| 11.6–14.6 years | 18 | 5.1 | 0.6 | 4.9 | 0.6 |
| 14.7–19.5 years | 7 | 4.8 | 0.5 | 4.6 | 0.5 |

[a]Significant interactions shown by Side by Diagnosis by Age ANOVA ($F=17.36$, $df=3, 86$, $p=0.02$), ANCOVA with total brain volume as covariate ($F=2.65$, $p=0.05$), and Side by Diagnosis ANOVA ($F=9.70$, $df=1, 86$, $p=0.01$) and ANCOVA ($F=6.00$, $p=0.02$).

0.07), and no significant effect in the groups of children aged 8.4 to 11.5 years.

Inspection of the means in table 2 suggests that caudate volumes decrease with increasing age in normal subjects. Correlations between age (used as a continuous variable) and caudate volumes showed that the caudate volumes decreased with increasing age in the normal subjects (right: $r=-0.38$; left: $r=-0.38$; $N=48$ and $p<0.006$ for both), but in the patients the caudate volumes did not decrease with age (right: $r=-0.10$, $N=50$, $p=0.47$; left: $r=-0.05$, $N=50$, $p=0.71$). Calculation of percentage change in caudate volume across our age range was based on the corresponding regression equations. Right caudate volume decreased by 9.4% and 16.0% in the patients and normal subjects, respectively, and the left caudate volume decreased by 8.7% and 16.6%.

### *Behavioral Measures*

For the ADHD group, the teacher and parent hyperactivity and conduct factor ratings and the Continuous Performance Test errors correlated significantly with each other, as expected, but when partial correlations were performed by using age, full-scale IQ, and total brain volume as covariates, we found no more significant correlations with caudate volumes or asymmetry than would be expected by chance at our predetermined alpha level of 0.01. Presence of reading or math learning disability or comorbid diagnosis of oppositional defiant disorder or mild conduct disorder also had no significant relationship to total brain volume, caudate volume, or symmetry.

## DISCUSSION

Using a large group of boys with ADHD and well-matched normal subjects, we found smaller total brain volumes and absence of normal caudate volume asymmetry (right greater than left) in the ADHD boys, which was accounted for both by smaller right caudates in the ADHD boys and by consistently larger caudates on the right side across all ages in the normal subjects. Differences in caudate asymmetry were not accounted for by total brain volume, IQ, or comorbid learning disabilities or other diagnoses involving disruptive behavior. In addition, while caudate volume decreased significantly with age in the comparison subjects, this was not true in the ADHD boys.

The highly significant difference in total brain volume between the ADHD boys and their matched comparison subjects is intriguing. While total brain volume did not affect the caudate asymmetry finding, it raises questions regarding other possible areas that may differentiate boys with ADHD. Volumetric measurements of cortical and subcortical regions are in progress and will bear on this question.

Theories of dyslexia have been informed by findings of left-greater-than-right cortical asymmetries in regions such as the planum temporale (30, 31). Asymmetries favoring the right hemisphere have not been reported as widely. However, the right frontal lobe is larger than the left in 80% of the 40 brains measured in the Yakovlev collection, and this asymmetry was confirmed in fetal brains as young as 20 weeks gestation (32). Hynd et al. (10) also found that normal children had a right-greater-than-left asymmetry in the frontal area of a single axial slice that was reversed in children with ADHD.

The caudate nuclei are integral elements of the dorsolateral and orbitofrontal cortical-striatal-thalamic loops that have been found to subserve executive function and delayed responding in primates (14, 33). Smaller right caudates and lack of normal caudate asymmetry in ADHD are consistent with the hypothesis that ADHD may reflect a right hemispheric dysfunction (34, 35). Right hemisphere attentional systems are preferentially activated in PET vigilance tasks (36, 37), and right-sided lesions are more likely to produce neglect syndromes and disruptions in attentional processing (38). Asymmetry in subcortical structures has not been extensively studied in humans or in the comparative literature. This may be in part due to the methodological difficulties involved. A brain can be sliced only once, surface landmarks can be deceiving, and making cuts that are precisely perpendicular to the axis of interest can be quite difficult. MRI allows much more flexibility and accuracy than is available even with some postmortem specimens since there is no processing artifact. Using MRI, two separate groups have found that the right caudate is significantly larger than the left in normal adults (39, 40). While our confirmation of this asymmetry in normal boys is statistically robust (42 of our 48 normal subjects had right caudates larger than the left), the absolute magnitude of the mean difference between caudate volumes is modest (4%), and an adequate number of subjects is required to demonstrate it. These issues and methodological differences (axial ver-

sus coronal views) may explain why caudate asymmetry was not detected in a recent contrast group of normal children (41). Caudate asymmetry has been recently examined by Hynd et al. in children with ADHD (13). In their group of 11 patients and 11 normal subjects, analysis of a single "best view" slice showed that eight of the 11 normal children had a left-greater-than-right pattern of head of caudate asymmetry and eight of the 11 patients had the opposite pattern. Our results contradict their findings. The asymmetry index in our 98 subjects ranged from 17.9% to −10.5%, whereas their range in 22 subjects was 52% to −60%. Their small group size and large variance suggest that this may be type I error. Replication with larger groups of subjects is needed to resolve this conflict.

Our other main finding relates to differences in brain development between normal subjects and ADHD subjects. Caudate volume decreases with increasing age in normal subjects but not in ADHD boys. The broad outlines of normal human brain development have been defined on the basis of work with primates (15, 42), infants (43), and children (44). Synaptogenesis increases logarithmically until a peak is reached at the equivalent of ages 1–3 years in humans. After that peak, the macaque, for example, loses an average of 32,700 synapses per second during the prepubertal period of 2.7 to 5.0 years of age (45). There are strong regional differences, however, in the rate of morphological change across our age range (our work in progress). Our findings of decreasing caudate volume with age in normal children replicate those of Jernigan et al. (46) and suggest that the caudate nuclei may be affected by decreases in trophic influences resulting from synaptic pruning across the broad age period of 5 to 18 years. In rodents, in contrast, caudate development plateaus at a much earlier stage (47). We speculate that the absence of a similar effect in ADHD children might indicate a diminished synaptic redundancy at earlier developmental periods. The diagnostic criteria for ADHD require that symptom onset take place before age 7, and most children are not diagnosed until they encounter the demands of an academic environment. However, most children who will go on to be diagnosed with ADHD are distinctly more active from toddlerhood, and in some cases from prenatal life (48). Most of the proposed etiologic factors in ADHD affect early brain development (1). We speculate that synaptic pruning may be ultimately more effective if it operates on a larger number of possible synaptic combinations. It may be this greater efficiency in normal subjects that produces the greater facility in attention and executive functioning that is apparently associated with asymmetric caudate development.

The finding of different anatomical brain structure in ADHD cannot be interpreted as proving etiological differences. The behaviors in ADHD, for example, could alter the stimulus input in the environment such that normal brain development is altered. It is possible that diminished attention span could inhibit the development of striatal cells monitoring sustained interactions with environmental stimuli. Finally, although chronic stimulant treatment has negligible effects on cerebral metabolism in adults with ADHD (49), the effects on basal ganglia volumes in children have not been assessed.

In conclusion, there are robust abnormalities in caudate asymmetry and in developmental changes in caudate volume across childhood and adolescence in ADHD, at least in boys. Studies of younger and drug-naive children and of girls with ADHD are underway to extend these findings. Anatomical imaging appears a promising tool for understanding the abnormal brain systems in this disorder, and a comprehensive study of regional brain differences is also ongoing. It may be that with a subtle disorder such as ADHD, which is characterized by various situation-specific behaviors that are hard to duplicate in a laboratory, anatomical studies may be useful in informing future functional studies, particularly those that use MRI.

## REFERENCES


1. Castellanos FX, Rapoport JL: Etiology of attention-deficit hyperactivity disorder. Child and Adolescent Psychiatr Clinics of North America 1992; 1:373–384
2. Faraone SV, Biederman J, Lehman BK, Keenan K, Norman D, Seidman LJ, Kolodny R, Kraus I, Perrin J, Chen WJ: Evidence for the independent familial transmission of attention deficit hyperactivity disorder and learning disabilities: results from a family genetic study. Am J Psychiatry 1993; 150:891–895
3. Faraone SV, Biederman J: Genetics of attention-deficit hyperactivity disorder. Child and Adolescent Psychiatr Clinics of North America 1994; 3:285–301
4. Lou HC, Henriksen L, Bruhn P: Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. Arch Neurol 1984; 41:825–829
5. Lou HC, Henriksen L, Bruhn P, Borner H, Nielsen JB: Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurol 1989; 46:48–52
6. Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, Hamburger SD, Cohen RM: Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 1990; 323:1361–1366
7. Matochik JA, Nordahl TE, Gross M, Semple WE, King AC, Cohen RM, Zametkin AJ: Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. Neuropsychopharmacology 1993; 8:377–386
8. Zametkin AJ, Liebenauer LL, Fitzgerald GA, King AC, Minkunas DV, Herscovitch P, Yamada EM, Cohen RM: Brain metabolism in teenagers with attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1993; 50:333–340
9. Matochik JA, Zametkin AJ, Liebenauer LL, Cohen RM: Effects of chronic stimulant treatment on cerebral metabolism in adults with hyperactivity. Society for Neuroscience Abstracts 1992; 18: 726
10. Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D: Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. Arch Neurol 1990; 47:919–926
11. Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D, Lyytinen H: Corpus callosum morphology in attention-deficit hyperactivity disorder: morphometric analysis of MRI. J Learning Disabilities 1991; 24:141–146
12. Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, Rapoport JL: Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am J Psychiatry 1994; 151:665–669
13. Hynd GW, Hern KL, Novey ES, Eliopulos D, Marshall R, Gon-

zalez JJ, Voeller KKS: Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol 1993; 8:339–347
14. Alexander GE, DeLong MR, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986; 9:357–381
15. Goldman-Rakic PS: Development of cortical circuitry and cognitive function. Child Dev 1987; 58:601–622
16. Chelune GJ, Ferguson W, Koon R, Dickey TO: Frontal lobe disinhibition in attention deficit disorder. Child Psychiatry Hum Dev 1986; 16:221–234
17. Shue KL, Douglas VI: Attention deficit hyperactivity disorder and the frontal lobe syndrome. Brain Cogn 1992; 20:104–124
18. Grodzinsky GM, Diamond R: Frontal lobe functioning in boys with attention-deficit hyperactivity disorder. Developmental Neuropsychology 1992; 8:427–445
19. Elia J, Borcherding BG, Rapoport JL, Keysor CS: Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res 1991; 36:141–155
20. Welner Z, Reich W, Herjanic B, Jung KG, Amado H: Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry 1987; 26:649–653
21. Woodcock RW, Johnson BB: Woodcock-Johnson Psychoeducational Battery. Allen, Tex, DLM Teaching Resources, 1977
22. Andreasen NC, Flaum M, Swayze V II, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WTC: Intelligence and brain structure in normal individuals. Am J Psychiatry 1993; 150:130–134
23. Jernigan TL, Tallal P: Late childhood changes in brain morphology observable with MRI. Dev Med Child Neurol 1990; 32:379–385
24. Werry JS, Sprague RL, Cohen MN: Conners' Teacher Rating Scale for use in drug studies with children—an empirical study. J Abnorm Child Psychol 1975; 3:217–229
25. Rosvold HE, Mirsky AF, Sarason I, Bransome ED Jr, Beck LH: A continuous performance test of brain damage. J Consult Psychol 1956; 20:343–350
26. Denckla MB: Revised Neurological Examination for Subtle Signs. Psychopharmacol Bull 1985; 21:773–800
27. Rasband W: NIH Image Manual. Bethesda, Md, National Institutes of Health, 1993
28. Williams PL, Warwick R, Dyson M, Bannister LH (eds): Gray's Anatomy, 37th ed. Edinburgh, Churchill Livingstone, 1989
29. SAS Language and Procedures: Usage, Version 6, 1st ed. Cary, NC, SAS Institute, 1989
30. Witelson SF: Cognitive neuroanatomy: a new era. Neurology 1992; 42:709–713
31. Rumsey JM, Dorwart R, Vermess M, Denckla MB, Kruesi MJP, Rapoport JL: Magnetic resonance imaging of brain anatomy in severe developmental dyslexia. Arch Neurol 1986; 43:1045–1046
32. Weinberger DR, Luchins DJ, Morihisa J, Wyatt RJ: Asymmetrical volumes of the right and left frontal and occipital regions of the human brain. Neurology 1982; 11:97–100
33. Yeterian EH, Van Hoesen GW: Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. Brain Res 1978; 139:43–63
34. Heilman KM, Voeller KK, Nadeau SE: A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J Child Neurol 1991; 6(suppl):S76–S81
35. Brumback RA, Staton RD: Right hemisphere involvement in learning disability, attention deficit disorder, and childhood major depressive disorder. Med Hypotheses 1982; 8:505–514
36. Pardo JV, Fox PT, Raichle ME: Localization of a human system for sustained attention by positron emission tomography. Nature 1991; 349:61–64
37. Cohen RM, Semple WE, Gross M, Holcomb HH, Dowling MS, Nordahl TE: Functional localization of sustained attention: comparison to sensory stimulation in the absence of instruction. Neuropsychiatry, Neuropsychology, and Behavioral Neurology 1988; 1:3–20
38. Mesulam MM: A cortical network for directed attention and unilateral neglect. Ann Neurol 1981; 10:309–325
39. Peterson BS, Riddle MA, Cohen DJ, Katz LD, Smith JC, Leckman JF: Human basal ganglia volume asymmetries on magnetic resonance images. Magn Reson Imaging 1993; 11:493–498
40. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F: Brain morphology and schizophrenia: a magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 1992; 49:921–926
41. Singer HS, Reiss AL, Brown JE, Aylward EH, Shih B, Chee E, Harris EL, Reader MJ, Chase GA, Bryan N, Denckla MB: Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology 1993; 43:950–956
42. LaMantia AS, Rakic P: Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. J Neurosci 1990; 10:2156–2175
43. Huttenlocher PR: Morphometric study of human cerebral cortex development. Neuropsychologia 1990; 28:517–527
44. Chugani HT, Phelps ME, Mazziotta JC: Positron emission tomography study of human brain functional development. Ann Neurol 1987; 22:487–497
45. Bourgeois JP, Rakic P: Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci 1993; 13:2801–2820
46. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA: Maturation of human cerebrum observed in vivo during adolescence. Brain 1991; 114:2037–2049
47. Fentress JC, Stanfield BB, Cowan WM: Observation on the development of the striatum in mice and rats. Anat Embryol (Berl) 1981; 163:275–298
48. Porrino LJ, Rapoport JL, Behar D, Sceery W, Ismond DR, Bunney WE Jr: A naturalistic assessment of the motor activity of hyperactive boys, I: comparison with normal controls. Arch Gen Psychiatry 1983; 40:681–687
49. Matochik JA, Liebenauer LL, King AC, Szymanski HV, Cohen RM, Zametkin AJ: Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. Am J Psychiatry 1994; 151:658–664